

A phase I trial of autologous and allogeneic bone marrow transplantation with genetically marked cells for the treatment of HIV associated lymphoid malignancies.

1. Introduction

1.1 Summary

Non-Hodgkins lymphoma (NHL) and Burkitt's lymphoma/leukemia are late complications of AIDS. However, they can present in patients with relatively preserved CD4 counts and/or be the first manifestation of AIDS. This seems to be more frequently the case in Burkitt's lymphoma/leukemia. For the purpose of this application we will designate all these lymphoid malignancies HIV associated NHL. HIV associated NHL often presents with extranodal disease, characteristically in the CNS, tends to respond poorly to conventional therapy and displays aggressive histology.

Allogeneic and syngeneic bone marrow transplantation have been previously attempted in patients with AIDS associated NHL (1-6). This experience, mostly accumulated during the era of zidovudine monotherapy, was disappointing although an autopsy study, which failed to find evidence of HIV-1 post-transplant, was provocative (7). Intriguingly, HIV infection and opportunistic fungal or bacterial infections were not the most common cause of death in patients undergoing BMT for HIV associated NHL. Rather, opportunistic lymphoma accounted for the negative outcomes.

Recent advances in the area of HIV virology and transplant biology led us to reconsider the use of autologous and allogeneic BMT for the treatment of HIV associated NHL. These are: I) highly active antiretroviral therapy (HAART), including protease inhibitors, allowing for drastic reductions in viral load, ii) the occasional occurrence of NHL in HIV+ individuals with relatively high CD4 counts, iii) recent evidence that sufficient number of progenitor cells with undetectable viral load can be obtained in HIV+ individuals for autologous transplantation, iv) the rapid immune and hematologic reconstitution that is seen after autologous and allogeneic transplantation of peripheral blood stem cells (PBSC), and v) the possibility to introduce HIV resistance genes into bone marrow cells.

This protocol will offer allogeneic BMT (for those patients with an HLA identical donor) or autologous BMT (for those without donor but with an HIV negative PBSC collection) for salvage treatment of HIV associated NHL or as part of initial therapy for patients with high risk HIV associated NHL. Both allogeneic and autologous transplants will be performed using conventional protocols but will require that patients have good performance status and low HIV viral load. A fraction of the stem cells used as a graft (not needed to assure engraftment) will be marked with a retrovirus containing anti-HIV genes and with an irrelevant retroviral control vector.

Retroviral transductions will be performed following protocols previously tested in humans at the NIH and elsewhere and utilized by us *in vitro* at Mount Sinai.

Vectors will be obtained from our collaborator, Richard A. Morgan, MD/Ph.D. (NIH,

National Human Genome Research Institute, Bethesda, MD) who is using the same vectors for an FDA approved human gene therapy trial to transduce syngeneic T-cells for uninfected twins into HIV-infected recipients.